Intravesical application of lidocaine and sodium bicarbonate in the treatment of obstructive idiopathic lower urinary tract disease in cats

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Abstract: BACKGROUND: In human patients with interstitial cystitis, intravesical instillation of alkalinized lidocaine sometimes is associated with sustained amelioration of symptoms beyond the acute treatment phase. Interstitial cystitis shares many features in common with feline idiopathic cystitis. OBJECTIVE: To evaluate whether intravesical instillation of alkalinized lidocaine decreases recurrence of urethral obstruction and severity of clinical signs in cats with obstructive idiopathic LUTD. ANIMALS: Twenty-six cats with obstructive idiopathic LUTD. Twelve cats in case group (treatment with alkalinized lidocaine) and 14 control cats (treatment with placebo or standard treatment). METHODS: Cats were randomly assigned to treatment (2 or 4 mg/kg lidocaine and sodium bicarbonate) or placebo groups (0.2 mL/kg saline solution and sodium bicarbonate). The intravesical instillation was done once a day for 3 days. Some cats underwent standard treatment only (indwelling urinary catheter for 3 days without intravesical instillations). A 2-week, 1-month, and 2-month follow-up after treatment was made using a questionnaire. The recurrence rate and amelioration scores of clinical signs were assessed and compared. RESULTS: Recurrence of urethral obstruction was 58% (7/12) in the case group and 57% (8/14) in the control group. Amelioration scores were similar between the 2 groups. CONCLUSION AND CLINICAL IMPORTANCE: Intravesical administration of lidocaine for up to 3 consecutive days had no apparent beneficial effect on decreasing recurrence rate and severity of clinical signs in cats with obstructive idiopathic LUTD.

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Title: Intravesical application of lidocaine and sodium bicarbonate in the treatment of obstructive, idiopathic lower urinary tract disease in cats

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Short title: Intravesical lidocaine in obstructive idiopathic LUTD

Keywords: indwelling urinary catheter, interstitial cystitis

Abbreviations: LUTD, lower urinary tract disease); IC, interstitial Cystitis; POD, post-obstructive diuresis)

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Background – In human patients with interstitial cystitis intravesical instillation of lidocaine and sodium bicarbonate sometimes is associated with sustained amelioration of symptoms beyond the acute treatment phase. Interstitial cystitis shares many features in common with feline idiopathic cystitis.

Objective – To evaluate whether the intravesical instillation of lidocaine in combination with sodium bicarbonate helps to reduce the recurrence of urethral obstructions and the severity of clinical signs in cats with obstructive, idiopathic LUTD.

Animals – Twenty-six cats with obstructive idiopathic LUTD. Twelve cats in the case group (treatment with alkalinized lidocaine) and 14 cats as controls (treatment with placebo or standard therapy).

Methods – Cats were randomly assigned to the treatment (2 or 4mg/kg lidocaine and sodium bicarbonate) or the placebo groups (0.2mL/kg saline solution and sodium bicarbonate). The intravesical instillation was done once a day for 3 days. Some cats underwent a standard treatment only (indwelling urinary catheter for 3 days without intravesical instillations). A 2 weeks, 1 month and 2 months follow-up after discharge of the cats with successful treatment was made using a questionnaire. The recurrence rate and the amelioration scores of the clinical signs were assessed and compared.

Results – The recurrence of urethral obstruction was 58% (7/12) in the case group and 57% (8/14) in the control group. The amelioration scores were similar between the two groups.

Conclusion and clinical importance – The intravesical administration of lidocaine for up to three consecutive days had no apparent beneficial effects on reducing the recurrence rate and the severity of clinical signs in cats with obstructive idiopathic LUTD

38 INTRODUCTION

39

40 The term feline lower urinary tract disease (LUTD) has been used to describe the clinical
41 signs related to irritative voiding, but does not identify the underlying etiology (Hostutler
42 et al., 2005; Forrester et al., 2007). The possible causes can include bacterial urinary tract
43 infection, trauma, urolithiasis, urethral plugs, neoplasia, anatomic malformation,
44 behavioral disorders and neurologic problems (Kruger et al., 2009; Hostutler et al., 2005).
45 If no specific reason is found, the disease is called idiopathic (Westropp et al., 2004).
46 Regardless of the etiology, the resultant clinical signs are similar and include dysuria,
47 stranguria, hematuria, pollakiuria and periuria (Forrester et al., 2007; Lekcharoensuk et
48 al., 2001). The uropathy can be obstructive and urethral obstruction was reported to occur
49 more commonly in young cats and almost exclusively in male cats due to their relatively
50 long and narrow urethra (Hostutler et al., 2005).
51 Recurrences of obstructions are common. In one study it was reported that 8 of 22 cats
52 (36%) with idiopathic urethral obstruction re-obstructed after a median of 17 days
53 (Gerber et al., 2008). In a more recent study, 11 of 55 cats (22%) with idiopathic
54 obstructive LUTD had experienced at least one recurrence within the 6 months after a
55 previous episode (Segev et al., 2011). Currently no treatment is known to reduce these
56 high recurrence rates.
57 A syndrome in human beings, known as interstitial cystitis (IC) shares many features in
58 common with cats having idiopathic cystitis (Buffington, 2011). The cause of IC is also
59 unknown and the treatment is mostly empirical and unsatisfactory (Moutzouris et al.,
60 2009). In a recent manufacturer funded study, the treatment with intravesical alkalinized

lidocaine (PSD597) and sodium bicarbonate in patients with IC was reported to provide amelioration of symptoms beyond the acute treatment phase (Nickel et al., 2009). IC is thought, in part, to develop into a visceral allodynia, as a result of sensitized local bladder afferent nerves (Butrick 2003). Theoretically, intravesical administration of the local anesthetic lidocaine could help to control the pain and inflammation associated with IC, returning the neuropathic bladder to a more normal state with time (Nickel et al., 2009). Because of the positive effects assessed in human medicine with the intravesical alkalinized lidocaine and the similarities reported between human IC and idiopathic LUTD, we hypothesized that cats with LUTD might also benefit from the lidocaine treatment. Because the obstructive form could become life threatening and the urinary catheter is necessary to relief the obstruction, the study was only conducted on cats with urethral obstruction. The aim of this prospective study was to determine whether the intravesical instillation of lidocaine could effectively reduce the severity of clinical signs or the recurrence rate of urethral obstruction in cats with obstructive, idiopathic LUTD.

MATERIALS AND METHODS

Case selection

Cats brought to the Clinic for Small Animal Internal Medicine, University of Zurich, between July 2010 and September 2011 showing one or more of the following clinical signs: pollakiuria, haematuria, dysuria, stranguria, inappropriate urination and with partial or complete urethral obstruction were considered to be included in the study. A cat

was regarded as obstructed if the bladder was distended and the cat was unable to void urine freely or only voided drops of urine.

The diagnostic investigation included anamnestic information from the owner regarding previous episodes of LUTD and observed clinical abnormalities, a physical examination, urinalysis, urine culture, hematology, serum biochemistry profile, radiographs of the abdomen (care was taken to include the entire lower urinary tract to the tip of the penis) and ultrasound of the urogenital tract. Urine was collected by cystocentesis or by catheterization. Qualitative urine culture was performed on sheep blood agar, Gassner agar and Clad agar[i]. If there was the suspicion of urethral stricture, or perforation of the lower urinary tract, contrast radiography (retrograde uretrography) was performed in addition.

Urolithiasis was diagnosed when stones were seen on radiographs or during ultrasound examination of the urinary tract. Urinary tract infection was diagnosed when the qualitative urine culture was positive. Urethral plug was diagnosed when a plug was identified during urethral catheterization. If the underlying cause of the obstruction could not be identified after appropriate evaluation, we used the term idiopathic LUTD as diagnosis. Only cats with the diagnosis idiopathic LUTD were allowed in the study.

Owner consent was obtained prior to initiation of the treatment with lidocaine. The government animal welfare authorities of the canton of Zurich, Switzerland, approved the treatment protocol used in the study.

Procedure

105 After the diagnostic investigation and the confirmation of the urethral obstruction an
106 intravenous fluids therapy was started. The cats were unblocked in a standard manner.
107 The cats were anesthetized with fentanyl[ii] (5µg/kg, IV) and midazolam[iii] (0.23mg/kg, IV)
108 or ketamine[iv] (IV or IM) and midazolam (0.23mg/kg, IV or IM) and kept under
109 anesthesia with propofol[v] injections or with inhalation anesthesia (isofloran[vi]) until an
110 indwelling urinary catheter[vii] was placed and sutured to the prepuce. When feasible, the
111 urinary catheter was maintained in place for 3 days. The urinary catherter was connected
112 to a sterile closed collection system[viii] to keep the bladder empty and to quantify urine
113 production. Cats were concurrently treated with an analgesic (buprenorphine[ix] 0.006-
114 0.014mg/kg IV q 6 h) and fluid was administered intravenously (lactated ringer's solution
115 or 0.9% saline solution)[x]. The initial infusion rate was determined based on the hydration
116 status and physical condition at presentation. The rate was daily adjusted also based on
117 the urine production assessed during the day.
118 The first 12 cats have been treated with the intravesical instillation of 2mg/kg 2%
119 (0.1mL/kg) lidocaine[xi], a dosage reported to be safe after intravenous application in a
120 recent study (Ko JC et al., 2008). Sodium bicarbonate[xii], 0.06mL/kg 8.4% was added
121 immediately after. Because no adverse events or side effects were seen, we decided to
122 increase the amount of lidocaine in the solution. Subsequently, the following cats were
123 randomly assigned to receive either intravesical 4mg/kg 2% lidocaine (0.2mL/kg) or
124 placebo (0.2mL/kg 0.9% saline solution) and 0.06mL/kg 8.4% sodium bicarbonate,
125 respectively. If the owners didn't want to join the study and/or if the cats were too
126 aggressive and uncooperative at the beginning of the treatment, the cats were treated

according to a standard procedure (3 days with indwelling urinary catheter without intravesical instillation).

The case group consisted of cats that received the intravesical medication of either 2 or 4mg/kg 2% lidocaine and 0.06mL/kg 8.4% sodium bicarbonate. The control group consisted of cats that either received the intravesical instillation of 0.2mL/kg placebo (equal volume as the instilled lidocaine 4mg/kg 2%) and 0.06mL/kg 8.4% sodium bicarbonate or that underwent the standard treatment. Before instillation the bladder was emptied and after instillation the urinary catheter was closed for 1 hour to leave the medication in place. After 1 hour the catheter was re-attached to the closed urine collection system and the urine production was assessed. This procedure was performed once a day for a maximum of 3 consecutive days.

After the removal of the urinary catheter, presence of spontaneous urination was assessed monitoring the cats every 2 hours over 1 or 2 days by a clear or unclear situation about their ability to void urine and consequently empty the bladder, respectively. An antibacterial treatment with amoxicillin-clavulanic acid[xiii] (20mg/kg q 12 h) or amoxicillin[xiv] (20mg/kg q 12 h) was concurrently started and continued in cats that did not re-obstruct immediately after removal of the urinary catheter.

Treatment success was defined as spontaneous urination (normal urine stream and emptied bladder after voiding) and consequently discharge from the hospital. Buprenorphine (0.006-0.014mg/kg PO q 8 h) or meloxicam suspension[xv] (0.025mg/kg, PO, q 24 h) in cats with and without azotemia at presentation, respectively, was prescribed for 3 additional days after discharge. The antibacterial treatment was continued for 1 week. Follow-up of cats with a successful treatment was made 2 weeks, 1

150 month and 2 months after discharge using a questionnaire to assess the severity of the
151 clinical signs after therapy.
152 Treatment failure was defined as failure to have spontaneous urination (unable to urinate
153 or only void drops of urine with a distended bladder consequently). These cats were
154 excluded from the follow-up assessment. Their owners were asked to complete only the
155 questionnaire for the clinical signs prior to treatment. A modified questionnaire
156 previously used in a study of Gunn-Moore et al., (2004) in cats with LUTD was used. All
157 the questionnaires were composed of 8 visual analogue scales, each 10 cm in length, with
158 values ranging from 0 (normal cat) to 10 (very severe symptoms). The 8 signs the owners
159 were asked to record were (i) increased frequency of urination, (ii) straining while
160 urinating, (iii) crying out while urinating, (iv) presence of blood in the urine
161 (macroscopic hematuria), (v) urination outside the litter box, (vi) increased grooming
162 around the perineum, (vii) altered behavior (as increased aggression/ fear/ nervous) and
163 (viii) gastrointestinal symptoms (vomiting or diarrhea).
164 The primary endpoint was the recurrence of urethral obstruction within 2 months after
165 removal of the catheter. The recurrence rate between groups was assessed and compared.
166 A secondary endpoint included the assessment of changes in severity (amelioration) of
167 clinical signs of LUTD from the baseline (prior to treatment), 2 weeks, 1 month and 2
168 months after discharge in cats with successful treatment. Because of the subjectivity of
169 the questionnaire, the median change from baseline (median amelioration scores) in the
170 single individual signs as well as in the sum of the 8 scales was calculated at each time
171 point. The differences between the groups were compared. The questionnaire prior to
172 treatment was filled in at least at the day of discharge.

Lidocaine serum concentrations

Blood samples for the evaluation of plasma lidocaine concentrations were collected from 2 cats treated with 2mg/kg lidocaine and 2 cats treated with 4mg/kg lidocaine at time 0+ h (immediately after instillation), 0.5 h, 1 h, 2 h and 3 h after treatment on 2 consecutive days of therapy. Plasma lidocaine concentrations were measured using high performance liquid chromatography-mass spectrometry. Any obvious clinical signs of side effects related to lidocaine toxicity were monitored and recorded every 2 hours during the hospitalization.

Statistical analysis

The results were analyzed using a commercial computer program (Statistical Package for Social Science 8.0; SPSS). Because of the small simple size, in particular by the follow up assessment, the comparisons of variables within and among groups were performed using a non-parametric test (the Mann-Whitney U test). The statistic analysis was not conducted if the available results to compare were less than 4. Differences were considered significant at $p<0.05$.

RESULTS

Overall, 69 cats were presented to the Clinic for Small Animal Internal Medicine, University of Zurich between July 2010 and September 2011 because of lower urinary tract signs with urethral obstruction. Thirty-four cats were excluded from the study

196 because of urolithiasis (N=13, 19%), urethral plugs (N=5, 7%) and urinary tract infection
197 (N=14, 20 %). In 2 cats (3%) a definitive diagnosis was not possible, because not all the
198 diagnostic investigations could be made. These 2 cats were also excluded from the study.
199 In 35 cats (51%) no specific cause for the clinical signs could be identified. These cats
200 were classified as having idiopathic obstructive LUTD. Of these 35 cats 9 were excluded
201 because of immediate surgery (perineale urethrostomy; 6 cats), urethral perforation after
202 catheterization (1 cat) and euthanasia wished by the owner (2 cats). Twenty-six cats
203 (33%) remained in the study.
204
205 The cats included in the study ranged in age from 1 to 9 years (median 5 years) and
206 weighted between 3.8 to 7.2 kg (median 5.5 kg). There were 25 neutered males and 1
207 intact male. The breeds included 20 domestic cats, 2 Persians, 1 Main Coon, 1 Siamese
208 and 2 Siberian Forest cats. BUN, creatinin and potassium ranged between 5.5 to
209 138mmol/L (median 12.6mmol/L), 70 to 1700µmol/L (median 150.5µmol/L) and 2.8 to
210 8.6mmol/L (median 4.5mmol/L), respectively. This was the first known episode of
211 LUTD for 21 cats whereas recurrent bouts were described for the 5 other cats. Twelve
212 cats were treated with 2% lidocaine (4 cats with 2mg/kg and 8 cats with 4mg/kg).
213 Fourteen cats were in the control group (8 cats were treated with placebo and 6 cats with
214 standard therapy). There was no significant difference in age, breed, BUN, creatinin,
215 potassium, or number of LUTD episodes between groups. Body weight was significantly
216 higher in the case group (p=0.04). The clinical signs score available from 10 cats in the
217 case group and 12 in the control group prior to treatment was not significantly different
218 between the two groups (Table 1). In 3 cats treated with 4mg/kg lidocaine and in 1 cat

219 treated with placebo the intravesical instillation was possible only for 2 days because of
220 the self-removal of the catheter after 2 days of therapy. In 1 cat treated with 4mg/kg
221 lidocaine the intravesical treatment was possible only for 1 day because of the aggressive
222 behavior of the cat after the first day of therapy. The median treatment duration in both
223 groups was 3 days. All the cats showed a post obstructive diuresis after relieving the
224 obstruction. In 24 cats the highest daily urine production was assessed; this ranged
225 between 2.2– 12.0mL/kg/h (median 6mL/kg/h). Additional, in 5 of the 26 cats, the urine
226 pH was measured at 1-hour immediately before re-attaching the urinary catheter to the
227 collection system. The pH value was 6, 7.5, 8.5 in three cats and 8 in other 2 cats.
228 The recurrence of urethral obstruction after removal of the urethral catheter was 58%
229 (7/12) in the case group (50% (2/4) in cats with 2mg/kg lidocaine, 63% (5/8) in cats with
230 4mg/kg lidocaine) within 1 - 14 days (median 3 days) and 57% (8/14) in the control
231 group (63% (5/8) in cats with placebo and 50% (3/6) in cats with standard therapy)
232 within 1 - 2 days (median 1 day). Five cats in the case group and 6 cats in control group
233 had a successful treatment for at least 2 months after discharge. These 11 cats were
234 followed up for the assessment of the amelioration in the clinical signs. Of all 11
235 questionnaires sent to the owners at each of three time points (2 weeks, 1 month and 2
236 months after discharge), 10 (4 of the case group and 6 of the control group), 10 (4 of the
237 case group and 6 of the control group) and 9 (4 of the case group and 5 of the control
238 group) were returned, respectively. The owners of the unavailable questionnaires were
239 followed up by phone to assess at least a new recurrence. In the case group, the degree of
240 severity in frequency of urination was not recorded in 1 questionnaire prior to treatment
241 as well as in another one 2 weeks and 2 months after treatment. For this clinical sign 2

242 weeks and 2 months after treatment the available results were insufficient to allow a
243 statistical analysis.
244 The cats treated with lidocaine showed a significantly higher median amelioration score
245 in straining while urinating 2 weeks after discharge compared to the cats in the control
246 group (p=0.01). There were no significant differences between groups in the other
247 individual clinical signs as well as in the sum of the scores at any time point.
248
249 ***Lidocaine serum levels***
250 In all cats the concentrations peaked within 60 minutes of instillation, ranging between
251 0.41 and 4.07µmol/L (Table 2). In all 4 cats blood sampling was not possible at all 5 time
252 points.
253 No severe adverse events were reported during the intravesical therapy. One cat treated
254 with 4mg/kg lidocaine showed one episode of salivation at the third day of treatment.
255
256 DISCUSSION
257
258 The response of cats with idiopathic obstructive LUTD on the lidocaine treatment with
259 regard to recurrence and amelioration in the clinical signs was poor. Within the 1-year
260 trial period recurrence of urethral obstruction was seen in 58% of the cats in the case
261 group and 57% in the control group within 2 months. In a previous 1-year study cats with
262 idiopathic obstructive LUTD experienced a recurrence rate of only 22% within 6 months
263 (Segev et al., 2010). It is unclear why the cats in the current study showed more
264 recurrence of the disease. It may reflect the different definition used to describe the

obstruction. In particular, in the current study a cat was defined as obstructed even if it was unable to express a normal stream of urine (only voided drops of urine) with a consequent distended bladder. It could also be that the observation of the clinicians and of the owners was closer because of the prospective study design and led to the recognition of even mild partial obstructions. Furthermore, the idiopathic LUTD was diagnosed by exclusion of other possible causes and as discussed in a prior study there remains always the question whether a specific cause was overlooked. It may be that a plug was not seen and was repulsed in the bladder after placement of the urinary catheter leading to a misdiagnosis of idiopathic LUTD (Gerber et al., 2008). Furthermore, a retrograde urethrography was only performed when leakage of the lower urinary tract was suspected. Anatomic malformations and strictures could not definitively be excluded in the cats in which urethrography was not performed.

A significant difference between groups in the follow-up assessment was only observed in the amelioration of straining while urinating 2 weeks after discharge. This significance may only be the consequence of statistical analysis conducted in several clinical signs all reflecting the same disease (type I statistical error). However, it might also reflect a limited potential effect of lidocaine, inducing only a relief from pain while urinating (stranguria) without inducing an adequate local anti-inflammatory effect. Lidocaine is primarily recognized as a neuronal sodium channel-blocking agent, but it also has proprieties capable of significant antihistamine effects. In an in vitro study, these effects were reported to be dose-dependent and at concentrations in the high micromolar range (234 to 2340μg/mL, 1000 to 10000μmol/L, respectively) (Yanagi et al., 1996). It could be supposed that a low serum lidocaine concentration is sufficient to have a neuronal

288 sodium-blocking effect (pain relief), while a very high tissue lidocaine concentration is
289 necessary to achieve antihistaminic effects (anti-inflammatory effect). The lack of a
290 demonstrable relevant beneficial effect could be related to subtherapeutic treatment
291 because of an inadequate dosage of lidocaine or sodium bicarbonate, inadequate duration
292 of the treatment, or because of the small sample size and insufficient power.
293 It is well known that cats may be more sensitive to the toxic effects of local anesthetics,
294 in particular to the central nervous system than are other species (Plumb 1999). However,
295 the cumulative doses of lidocaine in healthy cats were reported to be 9.7mg/kg at the
296 stage of excitation and 22.3 – 27.3mg/kg for the induction of convulsions (Seo et al.,
297 1982). The plasma lidocaine concentration associated with the onset of seizures was
298 reported to be between 71.3 – 208.5µg/mL (304.8 - 891.3µmol/L) (Chadwick, 1985).
299 Because side effects have also been observed after intravenous application of less than
300 2mg/kg lidocaine (Tilley et al., 1977) and because cats with cystitis have significantly
301 higher bladder permeability (Gao et al., 1994), the first cats of the current study were
302 treated with a dose of 2mg/kg lidocaine. The serum lidocaine level was assessed in 2 of
303 these cats. The concentration was well below to the plasma concentration reported to be
304 associated with the onset of seizures and the cats did not show any obvious side effects.
305 Therefore, the following cats were treated with a higher dose (4mg/kg) and even with this
306 dose a critical level was not reached. Only one cat showed one episode of salivation at the
307 third day of the lidocaine treatment. This cat was very stressed and the new environment
308 may have contributed to the salivation. Previous studies conducted in humans
309 demonstrated the poor absorption of lidocaine from the bladder and poor local therapeutic
310 effects if applied intravesically alone (Pode et al., 1992; Birch et al., 1994). Enhanced

absorption and therapeutic effects were reported alkalinizing the injected solution with sodium bicarbonate (Henry et al., 2001; Parsons 2005). Therefore, a sequential instillation of 0.06mL/kg sodium bicarbonate was added in all the cats receiving intravesical medication. However, voided bladder content pH, 1 hour after application was not basic in all the 5 cats in which it was measured. Furthermore, the lidocaine level in serum differed considerably between cats. A possible explanation could be the phenomenon of post-obstructive diuresis (urine output greater than 2mL/kg/h (Francis et al., 2010)). This pathophisiologic process could lead to relevant dilution of the urine, altering the urine pH and reducing the bladder lidocaine concentration within 1-hour after application. It is also possible that a longer duration of the treatment would have influenced the outcome. In studies of patients with IC an immediate and sustained symptomatic relief beyond the treatment phase was reported after 5 consecutive days of lidocaine instillations (Nickel et al., 2008) as well as after 6 instillations over 2 weeks (Parsons, 2005). Because the risk of physical and/or chemical injury to the urinary tract tissues and bacterial infections have been reported to increase with the duration of catheterization (Barsanti et al., 1985; Lees et al., 1984), the therapy in the current study was limited to a maximum of 3 days.

Important weaknesses of the study are the small sample size, in particular in the follow-up assessment. Furthermore, because of the uncooperative behavior of some cats the intravesical instillation was not always possible for 3 consecutive days. Moreover, only cooperative and not-aggressive cats at the beginning of the treatment as well as cats of owners that wanted to join the study were randomly assigned to the respective groups.

Furthermore, because a written consent by the owners of the cats treated with lidocaine was requested, we decided not to blind them. These attendant circumstances could have biased our results.

In conclusion, the current study shows an alternative procedure for the treatment of idiopathic cystitis in cats with urethral obstruction. The results suggest that the intravesical administration of lidocaine (2 or 4mg/kg) and sodium bicarbonate (0.06mL/kg) for 3 consecutive days does not have apparent beneficial effects on reducing the recurrence of new obstructions as well as the clinical signs in cats with idiopathic obstructive LUTD.

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[i] Oxoid, Pratteln, Switzerland

[ii] Sintenyl, Sintetica SA, Mendrisio, Switzerland

[iii] Dormicum®, Roche Pharma (Switzerland) AG, Reinach, Switzerland

[iv] Narketan®10, Vétoquinol AG, Ittingen, Switzerland.

[v] Propofol 1% MCT Fresenius, Fresenius Kabi (Switzerland) AG, Stans, Switzerland

[vi] Abbott AG, Baar, Switzerland

[vii] Portex®Jackson Cat Catheter, Smiths Medical International Ltd, UK / Slippery™Sam Tomcat Urethral Catheter, Smiths Medical PM Inc, Waukesha, Wisconsins.

[viii] Urotube®20, B. Braun Medical Meslungen GA, Melsungen, Germany.

[ix] Temgesic®, Reckitt Benckiser Healthcare Ltd, UK

[x] Fresenius Kabi GmbH, Hamburg, Germany

[xi] Lidocain HCL 2%, Kantonapotheke Zurich, Switzerland

[xii] B.Braun Medical AG, Sempach, Switzerland

[xiii] Clavubactin, Dr.E.Graeub AG, Bern, Switzerland

[xiv] Amoxicat40, Biokema SA, Crissier-Lausanne, Switzerland

[xv] Metacam®, Boehringer Ingelheim (Switzerland) GmbH, Basel, Switzerland